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## **Impact of obesity on stroke outcome after intravenous thrombolysis**

Sarikaya, H ; Elmas, F ; Arnold, M ; Georgiadis, D ; Baumgartner, R W

**Abstract:** BACKGROUND AND PURPOSE: Obesity is an established risk factor for stroke and has reached epidemic proportions. However, its impact on intravenous thrombolysis applied for acute ischemic stroke is not well known. We aimed to compare the clinical outcome and safety after intravenous thrombolysis in obese (body mass index  $\geq 30$  kg/m<sup>2</sup>) and nonobese (body mass index  $<30$  kg/m<sup>2</sup>) patients with ischemic stroke. METHODS: Data of 304 consecutive patients with stroke (251 nonobese and 53 obese) treated with intravenous thrombolysis were studied. We assessed the rate of favorable outcome (modified Rankin Scale score 0 or 1), mortality, and symptomatic intracranial hemorrhage in the 2 groups. RESULTS: Obese patients presented more often with diabetes mellitus (30.2% versus 12.4%,  $P<0.01$ ) and arterial hypertension (77.4% versus 61.4%,  $P=0.03$ ) as compared with their nonobese counterparts. At 3 months, the rate of favorable outcome was lower in obese compared with nonobese patients (50.9% versus 68.1%,  $P=0.02$ ). More obese than nonobese patients died (13.2% versus 4.0%,  $P=0.01$ ), whereas the rate of symptomatic intracranial hemorrhage was similar in the 2 groups (1.9% versus 1.6%,  $P=1.0$ ). After multivariable adjustment, obesity still remained an independent predictor of unfavorable outcome ( $P=0.04$ ) and mortality ( $P=0.04$ ). CONCLUSIONS: Our data indicate that obesity is an independent predictor of unfavorable clinical outcome and mortality in acute ischemic stroke treated with intravenous thrombolysis.

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# Impact of Obesity on Stroke Outcome

## After Intravenous Thrombolysis

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## **Background and Purpose**

Obesity is an established risk factor for stroke and has reached epidemic proportions. However, its impact on intravenous thrombolysis (IVT) applied for acute ischemic stroke is not well known. We aimed to compare the clinical outcome and safety after IVT in obese (body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>) and non-obese (BMI  $< 30$  kg/m<sup>2</sup>) patients with ischemic stroke.

## **Methods**

Data of 304 consecutive stroke patients (251 non-obese and 53 obese) treated with IVT were studied. We assessed the rate of favorable outcome (modified Rankin Scale score 0 or 1), mortality and symptomatic intracranial hemorrhage (sICH) in the two groups.

## **Results**

Obese patients presented more often with diabetes mellitus (30.2% vs. 12.4%,  $p < 0.01$ ) and arterial hypertension (77.4% vs. 61.4%,  $p = 0.03$ ) as compared with their non-obese counterparts. At three months, the rate of favorable outcome was lower in obese compared to non-obese patients (50.9% vs. 68.1%,  $p = 0.02$ ). More obese than non-obese patients died (13.2% vs. 4.0%,  $p = 0.01$ ), while the rate of sICH was similar in the two groups (1.9% vs. 1.6%,  $p = 1.0$ ). After multivariable adjustment, obesity still remained an independent predictor of unfavorable outcome ( $p = 0.04$ ) and mortality ( $p = 0.04$ ).

## **Conclusion**

Our data indicate that obesity is an independent predictor of unfavorable clinical outcome and mortality in acute ischemic stroke treated with IVT.

## 1 INTRODUCTION

2 Obesity is an established vascular risk factor with increasing prevalence and huge  
3 impact on public health worldwide.<sup>1</sup> It has been shown to be an independent predictor  
4 for ischemic stroke with an 4% risk increase for each unit augmentation in body mass  
5 index (BMI).<sup>2</sup> Thus, obese patients will constitute an increasing subgroup of candidates  
6 for intravenous thrombolysis (IVT). However, little is known about the impact of obesity  
7 on outcome in stroke patients treated with IVT. Therefore, we aimed to assess the  
8 clinical outcome and safety in obese and non-obese patients undergoing IVT for acute  
9 ischemic stroke.

## 11 METHODS

12 We studied prospectively collected data of consecutive patients with acute ischemic  
13 stroke who underwent IVT with alteplase, but no other or additional thrombolytic  
14 treatment at the University Hospital of Zurich between January 1, 2005, and November  
15 30, 2008. Routine baseline investigations and definition of variables have been  
16 reported in a previous study.<sup>3</sup> Body mass index was calculated as weight in kilograms  
17 divided by height squared in meters. Body weight and height were either obtained from  
18 the patient or the accompanying relatives at admission, or measured by nurse during  
19 hospital stay. Patients were classified as obese when BMI was 30 kg/m<sup>2</sup> or more.  
20 Intravenous thrombolysis was performed according to current guidelines except the use  
21 of extended time window up to 4.5 hours, the latter based on a pooled analysis  
22 presented at the 27th International Stroke Conference in February 2002 (San Antonio,  
23 Texas).<sup>4,5</sup> Patients and relatives were informed about the off-label use of alteplase  
24 beyond the 3-hour time window and informed consent was obtained prior to IVT. All  
25 patients were monitored in our stroke unit for at least 24 hours after thrombolysis. The  
26 study is approved by the local ethics committee.

## **Outcome measurements**

Symptomatic intracranial hemorrhage (sICH) was defined as neurological deterioration causing a  $\geq 4$  points worsening on the NIHSS causally related to ICH detected by CCT within 36 hours after initiation of IVT. Asymptomatic intracranial hemorrhage was defined as any ICH without neurological deterioration. Clinical outcomes were mortality and the modified Rankin Scale (mRS) score at 3 months, the latter dichotomized into favorable (0-1) and unfavorable (2-6).

## **Statistical analysis**

Statistical analysis was performed with SPSS 10.0 for Macintosh statistical software (SPSS Inc). Statistical significance for intergroup differences was assessed by the  $\chi^2$  or Fisher's exact test (the latter if some expected counts in the two-by-two table were too low) for categorical variables and the Mann-Whitney  $U$  test for continuous variables. Backward stepwise logistic regression analyses were performed to assess an independent association between obesity and the predefined endpoints. The variables included were age, gender, hypertension, diabetes mellitus, smoking status, baseline NIHSS score, time from stroke onset to treatment and pre-stroke treatment with antiplatelet agents. Significance was declared at 2-sided  $p < 0.05$  level.

## RESULTS

A total of 304 patients were eligible for this study; 53 (17%) of them were obese (mean BMI 33.2 kg/m<sup>2</sup>) and 251 (83%) non-obese (mean BMI 25.1 kg/m<sup>2</sup>). Obese patients presented more often with arterial hypertension and diabetes mellitus as compared with their non-obese counterparts, whereas age, stroke severity, time to treatment and other baseline characteristics were similar in both cohorts (Table). At three months, 27 of 53 (50.9%) obese and 171 of 251 (68.1%) non-obese patients experienced a favorable outcome ( $p=0.02$ ), while seven of 53 obese (13.2%) and 10 of 251 (4.0%) non-obese patients died ( $p=0.01$ ) (Figure). Symptomatic ICH occurred in one of 53 (1.9%) obese and 4 of 251 (1.6%) non-obese patients ( $p=1.0$ ), while asymptomatic ICH was observed in 7 of 53 (13.2%) obese and 35 of 251 (13.9%) non-obese patients ( $p=0.62$ ). Logistic regression analyses identified a higher baseline NIHSS score ( $p<0.01$ ) and obesity ( $p=0.04$ ) as independent predictors of unfavorable clinical outcome, whereas baseline NIHSS score ( $p<0.01$ ), age ( $p=0.01$ ), time to treatment ( $p=0.02$ ) and obesity ( $p=0.04$ ) predicted mortality independently.

## DISCUSSION

Our study suggests an adverse influence of obesity on IVT in ischemic stroke. Obese patients had less often a favorable outcome and were at higher mortality risk as compared with their non-obese counterparts. Logistic regression analyses suggest that the poor outcome in the obese cohort is independent from the associated vascular risk factors such as hypertension or diabetes mellitus.

Several reasons might explain the unfavorable clinical outcome in obese stroke patients treated with IVT. First, obesity has been shown to be associated with a proinflammatory and prothrombotic state,<sup>6,7</sup> thus potentially hampering the clot dissolving effect of alteplase. Plasminogen activator inhibitor-1 is a main inhibitor of fibrinolysis and seems to be consistently overexpressed in adipose tissue.<sup>8</sup> Furthermore, obesity is closely associated with the metabolic syndrome (MetS),<sup>9</sup> and the rate of MCA recanalization is lower in patients as compared to those without MetS.<sup>10</sup> Second, body weight was above 100 kg in 13 (25%) of obese patients; thus, the dose of alteplase might have been insufficient in these patients as the maximum dose is limited at 90 mg. In line with this, increased body weight in patients with acute myocardial infarction was associated with lower probability of coronary artery recanalization after IVT.<sup>11</sup> As pretreatment status of cerebral arteries and recanalization were unknown in our study, however, we have no means to support this hypothesis. Third, obese patients might be prone to more in-hospital complications such as venous thromboembolism.<sup>12</sup> In our study, obesity was associated with a higher mortality. This finding is in line with a previous study that reported a greater risk of all-cause and cardiovascular death among stroke patients with higher BMI.<sup>13</sup> The sICH risk in the obese cohort was similar compared to the non-obese patients. However, the low number of sICH precludes any definite conclusions on hemorrhage risk of IVT in obese stroke patients.

1           This study has some limitations. The cohort size of obese patients is small and  
2 does not allow to generalize our findings. Thus, our observation should be interpreted  
3 with caution and needs to be confirmed by further studies. Metabolic syndrome and  
4 hyperglycemia, both associated with obesity and higher resistance to IVT,<sup>10,14</sup> might  
5 have contributed to the effect of obesity. Another limitation of this study is that body  
6 weight and height were self-reported by patients or caregivers in part, although the  
7 validity of self reported measurements of body weight has been shown.<sup>15</sup> Finally, the  
8 outcomes were measured in clinical routine and thus were not necessarily obtained by  
9 blinded assessors.

10           In conclusion, our study suggests that obesity is an independent predictor of  
11 unfavorable clinical outcome and mortality in stroke patients treated with IVT. This  
12 observation might have a practical consequence as obesity may indicate a subgroup of  
13 patients with poor response to IVT, who may benefit from more aggressive treatment  
14 and monitoring strategies.



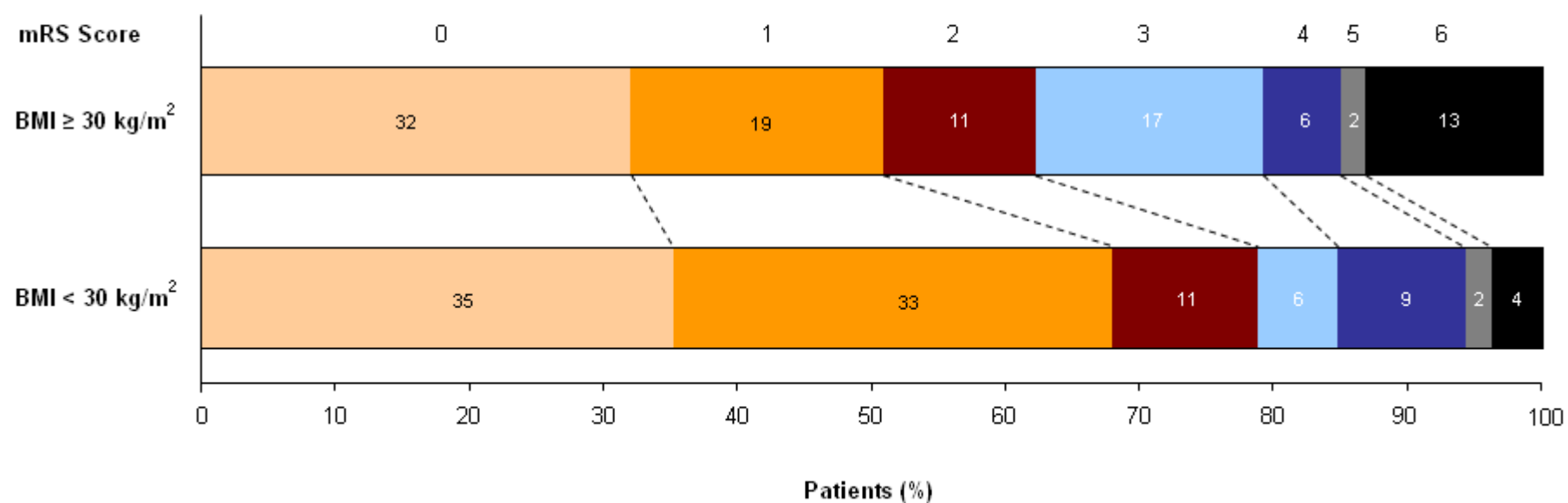
Table. Baseline Characteristics in Patients with BMI  $\geq 30$  kg/m<sup>2</sup> vs. BMI  $< 30$  kg/m<sup>2</sup>

	BMI $\geq 30$ kg/m <sup>2</sup> (n=53)	BMI $< 30$ kg/m <sup>2</sup> (n=251)	P Value
Mean age $\pm$ SD [years]	63.6 $\pm$ 13.6	63.6 $\pm$ 14.7	0.99
Male sex	62.3 (33)	66.1 (166)	0.63
Hypertension	77.4 (41)	61.4 (154)	0.03
Diabetes mellitus	30.2 (16)	12.4 (31)	<0.01
Coronary artery disease	15.1 (8)	17.1 (43)	0.84
Current smoking	28.3 (15)	26.7 (67)	0.87
Total Cholesterol $\pm$ SD [mmol/L]	5.2 $\pm$ 1.2	5.1 $\pm$ 1.2	0.52
Prestroke antiplatelet treatment	35.8 (19)	32.3 (81)	0.63
Admission systolic blood pressure $\pm$ SD [mmHg]	154.6 $\pm$ 23.1	154.1 $\pm$ 26.4	0.90
Admission diastolic blood pressure $\pm$ SD [mmHg]	87.8 $\pm$ 13.9	88.9 $\pm$ 14.2	0.66
Admission blood glucose $\pm$ SD [mmol/L]	7.2 $\pm$ 2.6	6.6 $\pm$ 2.3	0.12
Baseline NIHSS score $\pm$ SD	10.7 $\pm$ 5.9	10.0 $\pm$ 5.5	0.37
Stroke onset to treatment time $\pm$ SD [min]	161.3 $\pm$ 38.6	158.4 $\pm$ 43.0	0.65
Stroke subtype (TOAST-classification)			
Cardioembolism	49.1 (26)	53.0 (133)	0.09
Large-artery atherosclerosis	17.0 (9)	6.4 (16)	
Small-vessel disease	9.4 (5)	6.4 (16)	
Other determined etiology	3.8 (2)	5.2 (13)	
Undetermined etiology	20.7 (11)	29.0 (73)	

Values are % (n) unless noted otherwise.

SD standard deviation, NIHSS National Institutes of Health Stroke Scale

Figure. Proportion of obese ( $\text{BMI} \geq 30 \text{ kg/m}^2$ ) and non-obese ( $\text{BMI} < 30 \text{ kg/m}^2$ ) patients according to the modified Rankin Scale (mRS) scores at 3 months



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